

What is claimed is:

1. A method for identifying functional ligands for receptor proteins, said method comprising:
  - (a) isolating DNA sequences having a ligand-binding domain and a DNA-binding domain;
  - (b) constructing a chimeric gene by substituting operative portions of the DNA-binding domain region of the DNA sequence of step (a) with operative portions of a DNA-binding domain region from a known ligand-responsive receptor protein;
  - (c) introducing into a suitable receptor-deficient host cell:
    - (1) the chimeric gene from step (b), and (2) a reporter gene functionally linked to an operative hormone response element wherein the hormone response element is capable of being activated by the DNA-binding domain region of the receptor protein encoded by the chimeric gene of step (b);
  - (d) challenging the transfected host cell from step (c) with at least one compound to be evaluated for ligand binding activity with the chimeric receptor protein encoded by the chimeric gene of step (b);
  - (e) monitoring induction of the reporter gene; and
  - (f) identifying as a functional ligand(s) that ligand(s) which is capable of inducing production of the protein product of the reporter gene.

2. A method according to claim 1 (b) wherein the known ligand-responsive receptor protein is selected from the group consisting of glucocorticoid receptor, mineralocorticoid receptor, human thyroid receptors alpha and beta and rat thyroid receptor alpha, estrogen-related receptors hERR1 and hERR2, and retinoic acid receptors alpha and beta.

3. A method according to claim 1 (c) wherein the host cell is a COS cell.

4. A method according to claim 1 (c) (2) wherein the reporter gene is selected from the group consisting of a chloramphenicol acetyltransferase (CAT) gene and a firefly luciferase gene.

5. A method according to claim 1 (c) (2) wherein the hormone response element is selected from the group consisting of wild-type, recombinantly produced or synthetic (1) glucocorticoid response element, (2) thyroid response element, (3) mineralocorticoid response element, (4) estrogen-related response element, (5) retinoic acid response element, and (6) vitamin D<sub>3</sub> response element.

6. A method according to claim 5 wherein the glucocorticoid response element is encompassed within the mammary tumor virus long terminal repeat sequence (MTV LTR), and the thyroid response element is encompassed within the growth hormone promoter sequence.

7. A method for identifying functional ligands for receptor proteins in a cell wherein said cell contains,

- (a) an expressible chimeric DNA sequence (c) comprised of operative portions of a DNA-binding domain of a first receptor sequence linked to operative portions of a ligand-binding domain of a second receptor sequence, and (b) a reporter nucleic acid sequence functionally linked to an operative hormone response element wherein said chimeric DNA sequence is expressed and wherein the DNA-binding domain of the chimeric receptor protein thus produced can functionally bind to and activate the hormone response element that is functionally linked to the reporter sequence,

said method comprising challenging the cell with at least one compound to be evaluated for ligand binding activity wherein said compound to be evaluated is not known to be a functional ligand for the chimeric protein encoded by said chimeric DNA sequence (c).

8. A method of claim 7 wherein said cell is a COS cell.

9. A method according to claim 7 wherein the reporter gene is selected from the group consisting of a chloramphenicol acetyltransferase (CAT) gene and a firefly luciferase gene.

10. A method according to claim 7 wherein the hormone response element is selected from the group consisting of wild-type, recombinantly produced or synthetic (1) glucocorticoid response element, (2) thyroid response element, (3) mineralocorticoid response element, (4) estrogen-related response element, (5) retinoic acid response element, and (6) vitamin D<sub>3</sub> response element.

11. A method according to claim 10 wherein the glucocorticoid response element is encompassed within the mammary tumor virus long terminal repeat sequence (MTV LTR), and the thyroid response element is encompassed within the growth hormone promoter sequence.

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12. A method for identifying functional ligands for receptor proteins, said method comprising:

(a) isolating DNA sequences having a ligand-binding domain and a DNA-binding domain;

(b) constructing a chimeric gene by substituting operative portions of the DNA-binding domain region of the DNA sequence of step (a) with operative portions of a DNA-binding domain region from a known ligand-responsive receptor protein selected from the group consisting of hGR, hMR, hERR, hERR, rTR $\alpha$ , hT,R $\alpha$ , hT,R $\beta$ , hRAR $\alpha$ 1 and hRAR $\beta$ ;

(c) introducing into a suitable receptor-deficient host cell: (1) the chimeric gene from step (b), and (2) a reporter gene functionally linked to an operative hormone response element wherein the hormone response element is capable of being activated by the DNA-binding domain region of the receptor protein encoded by the chimeric gene of step (b) and is selected from the group consisting of wild-type, recombinantly produced or synthetic GR, PR, ER, T,R $\beta$  and V-erbA response element;

(d) challenging the transfected host cell from step (c) with at least one compound to be evaluated for ligand binding activity with the chimeric receptor protein encoded by the chimeric gene of step (b);

(e) monitoring induction of the reporter gene; and

(f) identifying as a functional ligand(s) that ligand(s) which induces production of the protein product of the reporter gene.

13. A method according to claim 12 wherein the glucocorticoid response element is encompassed within the mammary tumor virus long terminal repeat sequence (MTV LTR), and the thyroid response element is encompassed within the growth hormone promoter sequence.

14. A method for identifying functional ligands for receptor proteins in a cell wherein said cell contains: (a) an expressible chimeric DNA sequence (c) comprised of operative portions of a DNA-binding domain of a first receptor sequence linked to operative portions of a ligand-binding domain of a second receptor sequence, wherein said first and second receptor sequences are selected from the group consisting of sequences from hGR, hMR, hERR, hERR, rTR $\alpha$ , hT,R $\alpha$ , hT,R $\beta$ , hRAR $\alpha$ 1 and hRAR $\beta$ , and (b) a reporter nucleic acid sequence functionally linked to an operative hormone response element wherein said chimeric DNA sequence is expressed and wherein the DNA-binding domain of the chimeric receptor protein thus produced can functionally bind to and activate the hormone response element that is functionally linked to the reporter sequence, wherein the hormone response element is selected from the group consisting of wild-type, recombinantly produced or synthetic GR, PR, ER, T,R $\beta$  and V-erbA response element; said method comprising challenging the cell with at least one compound to be evaluated for ligand binding activity wherein said compound to be evaluated is not known to be a functional ligand for the chimeric protein encoded by said chimeric DNA sequence (c).

15. A method according to claim 14 wherein the glucocorticoid response element is encompassed within the mammary tumor virus long terminal repeat sequence (MTV LTR), and the thyroid response element is encompassed within the growth hormone promoter sequence.

TOTAL 1077304